

JUL. 19. 2004 7:24PM

BROWDY AND NEIMARK

NO. 4596 P. 1

RESPONSE UNDER 37 C.F.R. § 1.116
EXPEDITED PROCEDURE
EXAMINING GROUP 1600

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OFFICIAL

In Re Application of: Marina ZICHE et al

Art Unit: 1653

Application No.: 09/756,185

Conf. No. 5690

Examiner: R. Mitra

Filed: January 9, 2001

Washington, D.C.

For: COMPOUND B AS ANGIOGENIC AGENT IN COMBINATION WITH HUMAN GROWTH...

Atty.'s Docket: ZICHE-1

Date: July 19, 2004

THE COMMISSIONER OF PATENTS
2011 South Clark Place
Crystal Plaza Two, Lobby, Room 1B03
Arlington, VA 22202

Sir:

Transmitted herewith is a [] Amendment [X] Supplemental Response

in the above-identified application.

[] Small Entity Status: Applicant(s) claim small entity status. See 37 C.F.R. §1.27.

[XO] No additional fee is required.

[] The fee has been calculated as shown below:

	(Col. 1) CLAIMS REMAINING AFTER AMENDMENT	(Col. 2) MINUS	(Col. 3) HIGHEST NO. PREVIOUSLY PAID FOR	PRESNT EXTRA EQUALS
TOTAL	- 19	MINUS	-- 20	0
INDEP.	- 5	MINUS	*** 5	0
FIRST PRESENTATION OF MULTIPLE DEP. CLAIM				

SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X 9	\$		X 18	\$
X 42	\$		X 84	\$
+ 140	\$		+ 280	\$
ADDITIONAL FEE TOTAL			TOTAL	

- * If the entry in Col. 1 is less than the entry in Col. 2, write "0" in Col. 3.
- If the "Highest Number Previously Paid for" IN THIS SPACE is less than 20, write "20" in this space.
- *** If the "Highest Number Previously Paid for" IN THIS SPACE is less than 3, write "3" in this space.

The "Highest Number Previously Paid For" (total or independent) is the highest number found from the equivalent box in Col. 1 of a prior amendment of the number of claims originally filed.

[XO] Conditional Petition for Extension of Time

If any extension of time for a response is required, applicant requests that this be considered a petition therefor.

[] It is hereby petitioned for an extension of time in accordance with 37 CFR 1.136(a). The appropriate fee required by 37 CFR 1.17 is calculated as shown below:

Small Entity

Response Filed Within

- [] First - \$ 55.00
- [] Second - \$ 205.00
- [] Third - \$ 465.00
- [] Fourth - \$ 725.00

Month After Time Period Set

[] Less fees (\$ _____) already paid for _____ month(s) extension of time on _____

[] Please charge my Deposit Account No. 02-4035 in the amount of \$ _____

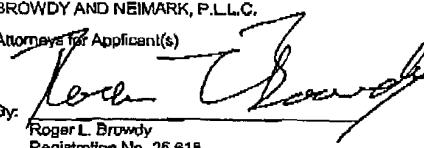
[] Credit Card Payment Form, PTO-2036, is attached, authorizing payment in the amount of _____

[] A check in the amount of \$ _____ is attached (check no. _____)

[XO] The Commissioner is hereby authorized and requested to charge any additional fees which may be required in connection with this application or credit any overpayment to Deposit Account No. 02-4035. This authorization and request is not limited to payment of all fees associated with this communication, including any Extension of Time fee, not covered by check or specific authorization, but is also intended to include all fees for the presentation of extra claims under 37 CFR §1.16 and all patent processing fees under 37 CFR §1.17 throughout the prosecution of the case. This blanket authorization does not include patent issue fees under 37 CFR §1.16.

BROWDY AND NEIMARK, P.L.L.C.

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JUL 19 2004 7:25PM

BROWDY AND NEIMARK

NO. 4596 P. 2

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Atty. Docket: ZICHE=1

OFFICIAL

In re Application of:) Conf. No.: 5690
Marina ZICHE et al)
Appln. No.: 09/756,185) Art Unit: 1653
Filed: January 9, 2001) Examiner: R. Mitra
For: COMPOUND B AS ANGIOGENIC) Washington, D.C.
AGENT IN COMBINATION WITH) July 19, 2004
HUMAN GROWTH FACTORS) VIA TELEFACSIMILE

SUPPLEMENTAL RESPONSE

Honorable Commissioner for Patents
U.S. Patent and Trademark Office
2011 South Clark Place
Customer Window, Mail Stop Non-Fee
Crystal Plaza Two, Lobby, Room 1B03
Arlington, VA 22202

Sir:

The present communication is intended to supplement the applicant's amendment of March 17, 2004, in response to the official action of December 17, 2003. Claims 3, 4, 6 and 10-25 presently appear in this case. No claims have been allowed, although it is noted that claims 4, 10, 13, 14, 15, 16, 17, 18, 21 and 22 have only been "rejected because they are dependent upon rejected claims." Reconsideration and allowance are hereby respectfully urged.

Following receipt of the advisory action of April 20, 2004, applicants requested and were granted an interview in this case, particularly in light of the fact that the

Appln. No. 09/756,185
Supplemental Response dated July 19, 2004
Reply to advisory action of April 20, 2004

examiner had not commented on applicant's arguments that unexpected results rebut a *prima facie* case of obviousness, and because applicant had unsuccessfully tried to schedule an interview in past, but acceptable times were unavailable. This interview was granted, and the undersigned thanks Examiners Mitra and Low for the courtesies extended during the interview that took place on May 13, 2004.

In the course of this interview, the undersigned explained why the combination of references cited by the examiner did not establish a *prima facie* case of obviousness. The examiners then advised applicant of U.S. patent 5,908,827 to Sirna. Although this patent is not of record in the case at the present time, the examiners pointed to column 6, line 41, which stated that component B can be useful in the therapy of pathologies correlated with altered levels of TGF- α , such as angiogenesis. It is respectfully requested that the examiners officially make this patent of record in this case, whether or not the present response is considered to place the case into condition for allowance. In view of this direct suggestion that component B would be expected to be useful in angiogenesis, applicants concede that if a new rejection were made which included this reference, a *prima facie* case of obviousness would be established for the coadministration of

Appln. No. 09/756,185
Supplemental Response dated July 19, 2004
Reply to advisory action of April 20, 2004

component B and human growth factor for the treatment of angiogenesis.

However, it was explained at the interview that the results shown in the present specification established that the results obtained using a combination of component B and human growth factor are synergistic in that the angiogenic score is significantly higher than what would be expected from the additive effects of the administration of each component individually. In the interview, the examiner objected to the reference in the previous amendment to an angiogenic score of 4.8 in Fig. 4B as this involved two pellets, while Fig. 4A involved only a single pellet. Nevertheless, the undersigned pointed out that, regardless of the significance of the results using the two pellets, it is clear from the open circle line in Fig. 4B, which is directly comparable with Fig. 4A, that significant synergistic properties are still shown. Note that the relevance of the two-pellets results is explained in the attached declaration of Dr. Ziche.

The examiners pointed out that the discussion of Fig. 4 at page 6 of the specification mentions P-values. The examiners suggested that applicant provide a graph of the results of these tests with bars showing the statistical measurements and indications of statistical significance. The examiners suggested that this data was needed in order to

Appln. No. 09/756,185
Supplemental Response dated July 19, 2004
Reply to advisory action of April 20, 2004

assess the argument that the results of the combination are statistically different from the expected combinatorial results of the two individual components.

Attached hereto is a declaration of Dr. Marina Ziche, under whose supervision the original tests shown in Fig. 4 were conducted. As requested by the examiners, attached to the declaration is a revised Figs. 4A and 4B. The declaration points out that the results were expressed as means for n=7 implants. Dr. Ziche states that multiple comparisons were performed by one-way ANOVA and individual differences were tested by Fisher's test after the demonstration of significant intergroup differences by ANOVA. A P-value of <0.05 was taken as significant. Dr. Ziche concluded that a P-value of <0.01, as reported in the two above described experiments, provided evidence for the synergy of the combination of component B and bFGF. This synergism was noteworthy and prompted the filing of the present application.

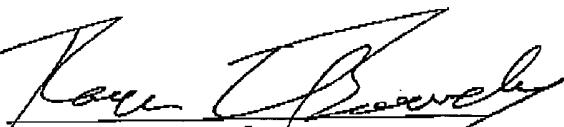
In view of this additional discussion of the results which were already in the present specification as filed, and which confirm the statements of statistical significance present in the specification, it is respectfully requested that the 35 U.S.C. § 103 rejection based on *prima facie* obviousness, both as appearing in the final rejection

Appln. No. 09/756,185
Supplemental Response dated July 19, 2004
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(Martelli in view of Folkman), and also any perspective rejection that includes Sirna, be withdrawn. The showing of record establishes unexpected results, both in the present specification and as supplemented by the explanatory declaration of Dr. Ziche. Reconsideration and allowance are therefore earnestly solicited.

Respectfully submitted,
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CERTIFICATE OF FACSIMILE TRANSMISSION

I hereby certify that this paper, including the attached declaration and Exhibit A thereto, is being facsimile transmitted to the Patent and Trademark Office at 703-872-9306, on the date shown below.

Jonathan Brammer
Name

Jon B
Signature

July 12, 2004
Date